Are you participating in any other research studies? _____ Yes _____No

This document is to be used as a guide for a discussion between you and your Study Doctor and the study team. This form, called an informed consent document, was designed to help you understand why this study is being done; what part of the study is "research" or "experimental;" what will be asked of you if you choose to participate; possible risks; any inconveniences or discomforts you may experience; and other important information. This form may also be helpful as a reference if you choose to participate, as a reminder of what your role in the study is, and who to contact if you have questions at any time during your participation. You are urged to discuss any and all questions you have about this study with members of the study team. If you wish, you can also discuss this study and your role with your family doctor or medical provider.

PURPOSE OF RESEARCH

You are invited to participate in a research study of a type of cancer found in the bones supporting your teeth (mandible and maxilla) called ameloblastoma. Ameloblastoma may also be known as "cystosarcoma;" "adamantine epithelioma;" and "adamantinoma." Ameloblastoma is a rare tumor of dental origin. We hope to learn how well pills called dabrafenib and trametinib dimethyl sulfoxide ("trametinib") work for the treatment of these types of tumors. You were selected as a possible participant in this study because you have been diagnosed with an ameloblastoma and your tumor has a mutation in a gene called BRAF. There is strong evidence in other diseases, especially melanoma, that the combination of dabrafenib and trametinib is effective in treating tumors with BRAF mutations, and preliminary evidence in ameloblastoma that the same is true.

Your normal medical care for ameloblastoma may include surgical removal of the tumor. Surgery is the standard treatment for these tumors if they are removable, and current therapies have had limited clinical benefit, with partial response being the best reported. It is unclear how much of the mandible and maxilla needs to be removed during surgery to prevent recurrence. Surgery is typically characterized as 2 options: conservative *vs* radical. Conservative surgery has a high rate of recurrence of the cancer (60 to 90%), and radical surgery tries to ensure that as much tumor as possible is removed, meaning that more tissue surrounding the tumor is removed ("wide margins" or borders), which may result in functional impediments to speech or swallowing, or be potentially-disfiguring.

The part of this study that is research (not part of your regular care) are the use of dabrafenib. Dabrafenib and trametinib will be provided at no cost to you.

If you decide to terminate your participation in this study, you should notify [redacted]

This research study is looking for about 5 research participants with BRAF-mutated ameloblastoma. Stanford University expects to enroll all 5 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

You will be informed of any significant new information about this study or the study drug dabrafenib that might affect your willingness to participate in this research study.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 36 months.

PROCEDURES

If you choose to participate, the Protocol Director and his research study staff will take a sample of blood to confirm your eligibility for this study. Once you have signed this informed consent document, the research team will perform the following procedures.

Baseline

At your first study visit, the study team will take measurements of your cancer growth. All of the below procedures are standard procedures necessary to determine your health and extent and characteristics of your tumor prior to treatment initiation. These procedures include:

- Tumor biopsy
- Imaging procedure (CT scan or MRI scan or x-ray)
- Clinical assessment with an ear/nose/throat specialist as well as a medical oncologist
- Eye exam

First 6 Weeks

After the baseline visit, all patients will initially begin taking dabrafenib, 150 mg twice-daily and trametinib, 2 mg once-daily by mouth for 6 weeks. <u>These medications must be taken at least 1 hour before or at least 2 hours after a meal.</u> After 6 weeks on the study, you will have an eye exam.

Tumor Resection (tumor surgically removed)

If your tumor will be surgically removed, you will continue twice daily dosage of study drugs until your surgery between weeks 6 and 7, including the day of your surgery.

If the surgeon is able to completely remove your tumor, you will discontinue taking dabrafenib and trametinib at that time. You will need to have another CT or MRI scan performed at this time order to assess both changes in your tumor extent and whether those changes will help guide the details of the surgery to be performed.

If the surgeon does not remove the entire tumor, you will have the option to resume dabrafenib and trametinib at your previous dose if:

- You did not previously need to discontinue dabrafenib and trametinib due to an adverse events or disease progression
- Your surgery recovery did not include any unexpected complications
- At least 1 week but no more than 6 weeks has passed since your surgery.

No Tumor Resection (tumor not surgically removed)

If your tumor will be not surgically removed (in all or part), a tumor biopsy will be conducted at about Week 7.

If there is no surgical option for your tumor, you may continue taking the study drugs until:

- Your disease progresses (worsens);
- You experience an adverse event or negative side-effect;
- You are willing to continue taking the study drug.
- You will be asked to have follow-up biopsies done to look for molecular changes in the tumor caused by dabrafenib and trametinib and for evidence of anti- tumor effects. This biopsy may be part of standard of care if we are unable to determine by other means (physical examination and scans) whether your tumor is responding. However, even if we can determine by other means that your tumor is responding, we would ask that you give your permission for a biopsy for research purposes alone. In this case, this second biopsy would be optional. We will make clear to you at the time of the proposed biopsy whether it is being done to help care for you and make care decisions or if it is only for research. The details concerning the risks and consent for the procedure itself will be covered by another consent process between you and the physician who is to perform the procedure.

During the study, you may need to have a vision exam to check for, or evaluate, possible vision effects associated with the study treatment. These exams, if needed, are regular medical care for patients receiving these treatments.

Prohibited Medications

In order to participate in this study, there are some medications that you may not take or only taken with caution. Please be sure to tell your doctor all medications and supplements you are currently taking, even if they are over-the-counter (OTC).

Prohibited medications include:

- Other anti-cancer therapies;

- Anti-retroviral drugs (Note: Subjects with known HIV are ineligible for study participation)
- Other investigational drugs;
- Herbal remedies (e.g., St John's wort).

Other Prohibited Medications	
Drug Class	**Drugs**
Antibiotics	Rifamycin class agents (eg, rifampin, rifabutin, rifapentine), Clarithromycin, telithromycin, troleandomycin
Anticonvulsant	Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Antiretroviral	Ritonavir, saquinavir, atazanavir
Hyperlipidemia	Gemfibrozil
Miscellaneous	Conivaptan, bosentan, St John's wort

Additionally, the following medications should be taken with caution. Please be sure to tell your study doctor if you are taking any of the following medications:

- Warfarin
- Medicinal products that decrease the stomach's acidity (or drugs that increase the pH in your stomach)

There is a long list of other medications that must be used in caution while taking dabrafenib and trametinib. The healthcare provider taking your initial history and physical will review your current prescription medication list, and in addition, all vitamins, herbals, and over-the-counter medications. That individual will provide guidance regarding these medications.

Long-term Follow-up

You will be followed for at least four weeks after your last dabrafenib dose to ensure you do not develop any side effects.

You should have an eye exam every year after the study.

MRI (Magnetic Resonance Imaging)

MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for a certain amount of time while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs or headphones that you will be required to wear. The space

within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

Risks:

Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

Your Tissue / Data Samples for Research and Genetic Testing

Research using tissues, such as from your tumor, is an important way to try to understand human disease. Sometimes, research may include the testing and study of genes, also known as DNA. This type of testing is also called “genetic analysis” or called “pharmacogenomic research.” You are been given this information because the Study Doctors want to include a sample of your tumor in a research project and because they want to save the samples for future research. This research may include trying to make cells from your tumor grow in the laboratory for further study.

There are several things you should know before participating in this study and allowing your tissues to be studied. This subject is complicated, and there are many considerations. Ask for more information if you do not understand any part of this information.

Genes are in every cell of your body. Your genes were inherited from your biological parents and carry instructions for the body to grow, develop, and survive. Genes are made of a substance called DNA. Most genes and DNA are identical among human beings, but there are small variations between different people. These small genetic differences are why people have their own unique characteristics, such hair color, eye color, height, and other characteristics. Some traits affected by genetics are not visible, such why different people have different responses, including side effects, to the same drug, or are more likely to get certain diseases or conditions. The proteins in your body were determined by your genes, and control how your body works. Differences in genes and therefore proteins can affect the way a disease develops, the way drugs act against the disease, or the way your body uses the drugs.

The purpose of this type of research is to understand the cause of disease, such as cancer, or the body's response to the treatments (such as safety findings or drug level patterns). In this study, the genetic research is being done to help identify individuals who will benefit more from using the study drug when their cancer returns around the same location or occurs in distant organs. to find out if the study medications (or other drugs) are effective against your cancer, why they were or weren't effective, and if there are any characteristics of the cancer that predicted whether or not the drugs would be effective.

Agreeing to provide this tumor biopsy sample is optional, and not required to participate in this study.

The data from your sample for this genetic research project will be used for research purposes only. The sample and data generated from them will be held by the study team and other researchers for many years. These samples, and the data generated from them, may be shared with other researchers or entered into databases, provided confidentiality is upheld (you are not identified), and they are used only for research on the topics described in this document. The information in these databases may be kept forever, however, information that could directly identify you will not be included in these databases.

Information from analyses of your coded samples and your coded medical information will be put into one of the National Institutes of Health (NIH) databases, such as the "database of Genotypes and Phenotypes" (dbGaP at http://www.ncbi.nlm.nih.gov/gap), along with information from the other research participants and will be used for future research. These databases will be accessible by the Internet. Only anonymous information from the analyses will be put in a completely public database, available to anyone on the Internet.

No traditionally-used identifying information about you, such as your name; address; telephone number; or Social Security Number, will be put into the public database. While the public database will not contain information that is traditionally used to identify you, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

However, your privacy is very important to us and we will use safety measures to protect it. Despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

Although you will be told the results of study tests that are part of your regular medical care, the genetic testing described here will not be used for decisions about your medical care, and there may be no results from this genetic research for

many years, therefore the results of the genetic testing may not be given to you, your doctor, or any other staff at the study center.

Providing genetic information to others

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

Be aware that that GINA 2008 does not specifically protect you against genetic discrimination by companies that sell life insurance; disability insurance; or long-term care insurance.

You have the right to refuse to allow your tissues to be studied now or saved for future study. You may withdraw from this study at any time. The Study Doctors might retain the identified samples, eg, as part of your routine clinical care, but not for additional research.

You do not have to agree to have us save your tumor tissue for these genetic research studies in order to participate in this trial. Your decision will not affect your participation to the rest of the study.

Please make your choice and initial one of the statements below:

_____ (initials) I agree (consent) to provide the tumor sample for described genetic research. The data from the tumor sample may be used in future genetic research.

_____ (initials) I **DO NOT** agree (consent) to provide the tumor sample for described genetic research.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Tell your doctor now if:
  - You have had cancer in the past
  - You are being treated for high blood pressure.
  - You have had an irregular heartbeat; heart failure; shortness of breath; swelling in your legs; or tiredness

- Contact your Study Doctor or the Study Team immediately if you experience:
  - Fever
  - Severe abdominal pain or sick to your stomach
  - Not wanting to eat (loss of appetite)
  - Blurry vision
  - Extreme tiredness
  - Fainting
  - Change in vision
  - Yellow eyes or skin
  - Itching
  - Easy bruising
  - Dark urine
  - Confusion
- Take the study drug as instructed.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Keep the study drug in a safe place, away from children and for your use only.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify [redacted]

If you withdraw from the study, or the study medication is stopped for any reason, it is important to tell the study doctor so any potential risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing might be most helpful for you.

If you decide to stop being in this study or if your study doctor withdraws you from taking part in this study, your study doctor will ask you to come back for a final study visit.

The Protocol Director may also withdraw you from the study and the study medication may be stopped without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.

- Pregnancy.
- You need treatment not allowed in the study.
- Your cancer worsens.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

You may have side effects from the medication or procedures used in this study and they will vary from person to person. Everyone taking part in this study will be watched carefully for any side effects. Stanford University, the study doctor and other doctors do not know all of the side effects that could occur and there may be unknown side effects that could occur. You should talk to your study doctor about any side effects that you have while taking part in this study.

Dabrafenib + Trametinib Combination side effects:

Approximately 3000 study participants have received the combination of dabrafenib and trametinib dimethyl sulfoxide “trametinib” at varying doses in other studies. The side effects listed below are primarily based on a total number of 559 patients studied in two phase 3 trials (MEK115306 and MEK116513). Tell your study doctor if you get any of these, or other, side effects.

VERY COMMON DABRAFENIB + TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS In 100 people receiving the combination of dabrafenib+trametinib, 10 or more (≥ 10%; 1 or more of every 10) may have:
• Fever, which may sometimes be associated with low blood pressure (hypotension), dehydration; dizziness; and/or fainting. • Bleeding (hemorrhage). The majority of events reported were mild bleeding events which did not require intervention; however, major bleeding events, defined as symptomatic bleeding in a critical area or organ, and/or fatal bleeding in the brain have been reported. • Chills • Decreased appetite • Headache • Dizziness • Cough • Abdominal pain • Constipation • Diarrhea • Nausea • Vomiting

VERY COMMON DABRAFENIB + TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS
In 100 people receiving the combination of dabrafenib+trametinib,
10 or more (≥ 10%; 1 or more of every 10) may have:

- Skin effects including:
  - Rash
  - Dryness
  - Itching
- Pain or stiffness of joint(s)
- Muscle pain
- Pain in arms or legs
- Feeling tired
- Feeling weak
- Swelling of your arms and/or legs (peripheral edema)
- Abnormal liver tests (ALT increased, AST increased) which may mean that your liver is not working normally.
  - This is usually mild and reversible, but it may be serious or life-threatening
  - Your study doctor will check liver tests regularly while you receive study treatment. Tell your study doctor or study nurse if you have itching, yellowing of the eyes or skin, dark urine, pain or discomfort in the right upper area of your stomach
- High blood pressure
  - Tell your study doctor if you are being treated for high blood pressure
- Inflammation of the throat and nasal passage (nasopharyngitis)

COMMON DABRAFENIB + TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS
In 100 people receiving the combination of dabrafenib+trametinib,
between 1 and 10 people (1 to 10%) may have:

- A type of skin cancer called squamous cell carcinoma (SCC)
- Thickening of the palms and soles, which may be tender or painful with a burning feeling (hand-foot skin reaction)
- Skin effects including:
  - Thickening of the skin (hyperkeratosis)
  - Skin cracking
  - Warts (papilloma)
  - Wart-like growths (seborrheic keratosis)
  - Skin lesions
  - Acne-like rash
  - Scaly patches (actinic keratosis)
  - Redness
  - Rash with pus-filled lesions
  - Inflammation of the fatty layer under the skin (panniculitis), which can cause red, painful lumps
- Skin infection (cellulitis)
- Dry Mouth
- Dehydration
- Night sweats
- Muscle spasms

COMMON DABRAFENIB + TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving the combination of dabrafenib+trametinib, between 1 and 10 people (1 to 10%) may have:

- Bladder infection
- Nail problems including pain infection and swelling of the cuticles (paronychia)
- Low number of platelets (thrombocytopenia), which may cause bleeding and bruising
- A decrease in white blood cell count (neutropenia) which may affect your ability to fight infection
- A decrease in red blood cells which may cause tiredness, shortness of breath or dizziness (anemia)
- Low blood sodium level often associated with dehydration (hyponatremia)
- Low phosphate level which may cause muscle weakness (hypophosphatemia)
- High blood sugar (hyperglycemia)
- Decrease in the number of white blood cells found in the blood (leukopenia)
- Eye problems such as blurry vision or vision changes
- Low blood pressure
- Swelling in an arm or leg as a result of fluid build-up (lymphedema)
- Facial swelling
- Shortness of breath (dyspnea)
- Redness, swelling or pain in the mouth (stomatitis)
- Hair loss
- Sweating more than usual
- Kidney failure
- Swelling of and/or redness and/or pain of the lining inside the mouth or nose or sometimes around the eyes (mucosal inflammation)
- Flu-like illness
- Inflammation of one or more hair follicles (folliculitis)
- Increased blood level of protein from the muscle (blood creatine phosphokinase increased)
- Abnormal liver tests (blood gamma-glutamyl transferase increased, blood alkaline phosphatase increased) which may mean that your liver is not working normally.
  - This is usually mild and reversible, but it may be serious or life-threatening.
  - Your study doctor will check liver tests regularly while you receive study treatment. Tell your study doctor or study nurse if you have itching, yellowing of the eyes or skin, dark urine, pain or discomfort in the right upper area of your stomach.
- Decreased heart rate (bradycardia)
- Changes in how well the heart pumps blood (ejection fraction decreased). This may cause an irregular heartbeat; heart failure; shortness of breath; swelling in your legs; or tiredness.
  - Tell your study doctor if you get any of these symptoms. Your study doctor will run tests to check your heart is working properly before and during treatment. It is also important to tell your study doctor about any pre-existing heart conditions.

UNCOMMON (RARE) DABRAFENIB + TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS

In ***1000*** people receiving the combination of dabrafenib+trametinib,

between 1 and 10 people (0.1 to 1%) may have:

- Allergic reaction
- New melanomas
- Skin tags (acrochordon)
- Problems with your eyes including:
- Retinal detachment
- Inflammation of the eye (uveitis)
- Swelling around the eyes (periorbital edema)
- Separation of light sensitive layer of the eye (the retina) from its supporting layers (retinal pigment epithelial detachment, chorioretinopathy) which can result in blurry vision.
- These types of vision problems often improve, however there is a slight risk that they may not improve and could lead to blindness
- Heart failure (cardiac failure, left ventricular dysfunction) which means the heart is not able to pump blood properly or it has difficulty filling with blood. It can cause weakness and tiredness, swelling, and shortness of breath.
- Inflammation of the pancreas, a gland that controls blood sugar levels and helps digest food
- Inflammation of the kidney (may appear as side pain or blood in the urine) (nephritis)
- Acute kidney failure
- Breakdown of muscle, which can lead to symptoms including muscle pain and kidney damage (rhabdomyolysis)
- Inflammation of the lung tissue (Pneumonitis or Interstitial lung disease) – may present with symptoms such as shortness of breath, changes in chest CT scan
- Tell your study doctor about any pre-existing lung problems that you have.
- Tell your study doctor if you have any new or worsening symptoms of lung or breathing problems, including:
- shortness of breath
- cough
- If your study doctor thinks you have signs or symptoms of impaired lung function, he/she may order more test(s) to further evaluate your lung function

Dabrafenib side effects:

Approximately 9600 cancer patients have been treated with dabrafenib alone or in combination with trametinib. Based on data from ongoing and completed studies, as well as post-marketing reports, the following are possible risks while taking dabrafenib.

VERY COMMON DABRAFENIB SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving dabrafenib, 10 or more (≥ 10%; 1 or more of every 10) may have:

- Diarrhea
- Nausea
- Vomiting
- Decreased appetite
- Skin effects including:
  - Rash
  - Thickening of the skin (hyperkeratosis)

VERY COMMON DABRAFENIB SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving dabrafenib, 10 or more (≥ 10%; 1 or more of every 10) may have:

- Warts (papilloma)
- Thickening of the palms and soles, which may be tender or painful with a burning feeling (hand-foot skin reaction, palmar-plantar erythrodysaesthesia syndrome)
- Hair loss (alopecia)
- Tiredness (fatigue)
- Headache
- Fever (pyrexia), which may sometimes be associated with low blood pressure, dehydration. dizziness and/or fainting
- Pain or stiffness of joint(s) (arthralgia)
- Muscle pain (myalgia)
- Pain in your arms and/or legs
- Chills
- Cough
- Weakness (asthenia)

COMMON DABRAFENIB SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving dabrafenib, between 1 and 10 people (1 to 10%) may have:

- Low phosphorous level which may cause muscle weakness (hypophosphatemia)
- Constipation
- Flu-like illness
- Cutaneous squamous cell carcinoma (SCC) of the skin (a type of skin cancer) / keratoacanthoma / Bowen's disease)
- Inflammation of the throat and nasal passage (nasopharyngitis)
- High blood sugar (hyperglycemia, may cause increased thirst and frequent urination)
- Skin effects including noncancerous skin growths, such as:
  - Skin lesions
  - Skin tags or wart-like growths (acrochordon, seborrhoeic keratosis)
  - Dry skin
  - Redness of the skin (erythema)
  - Itchy skin (pruritis)
  - Scaly skin (actinic keratosis)

UNCOMMON (RARE) DABRAFENIB SIDE EFFECTS, SOME MAY BE SERIOUS

In ***1000*** people receiving dabrafenib, between 1 and 10 people (0.1 to 1%) may have:

- Inflammation of the pancreas (pancreatitis), a gland that controls blood sugar levels and helps digest food
- Inflammation of the eye (uveitis), which can infrequently result in blindness. Tell your doctor about any changes in your vision
- Allergic reaction to dabrafenib which may appear as rash, blisters or fever
- New melanomas
- Kidney failure
- Inflammation of the fatty layer under the skin, which can cause red, painful lumps (panniculitis)

VERY RARE DABRAFENIB SIDE EFFECTS, SOME MAY BE SERIOUS

In ***10000*** people receiving dabrafenib, between 1 and 10 people (0.1 to 1%) may have::

- In a study of patients with melanoma brain metastases there have been reports of side effects in the brain (some of them fatal), including bleeding into the brain and seizures. These events may also be seen in patients with melanoma brain metastases who are not receiving dabrafenib.
- Inflammation of the kidney (may appear as side pain or blood in the urine) (nephritis)

OTHER DABRAFENIB SIDE EFFECTS, SOME MAY BE SERIOUS :

- In a study of patients with melanoma brain metastases there have been reports of side effects in the brain (some of them fatal), including bleeding into the brain and seizures. These events may also be seen in patients with melanoma brain metastases who are not receiving dabrafenib.

Trametinib side effects:

VERY COMMON TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving trametinib, 10 or more (≥ 10%; 1 or more of every 10) may have:

- Skin rash or acne-like rash:
  - Contact your study doctor or study nurse if you are affected, as it is important that this is treated to avoid more severe symptoms
- Diarrhea
  - Contact your study doctor or study nurse if you are affected, as it is important that this is treated to avoid dehydration
- Bleeding (hemorrhage)
  - The majority of events reported were mild bleeding events which did not require intervention. Major bleeding events in a critical area or organ, and fatal bleeding in the brain, have also been reported.
- Feeling sick (nausea)
- Feeling tired (fatigue)
- Swelling of the hands/feet (peripheral edema)
- Increase of blood pressure
  - Tell your study doctor if you have hypertension or are on medications to treat high blood pressure
- Vomiting
- Constipation
- Stomach pain
- Shortness of breath
- Cough
- Dry or itching skin
- Fever
- Dry mouth
- Unusual hair loss or hair thinning

COMMON TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving trametinib, between 1 and 10 people (1 to 10%) may have:

COMMON TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS

In 100 people receiving trametinib, between 1 and 10 people (1 to 10%) may have:

- Visual problems, such as blurry vision, and decreased vision:
  - Tell your study doctor about any changes in your vision; your study doctor will send you for eye exam and treatment may need to be interrupted. A blood sample will also be collected if you have vision problem to evaluate the amount of drug in your blood.
  - It is important that you do not drive a car or work with machinery if you are experiencing any visual changes.
  - These symptoms go away in most cases.
- Facial swelling
- Swelling around the eyes (periorbital edema)
- Dehydration (low levels of water or fluid)
- Swelling of and/or redness and/or pain of the lining inside the mouth or nose (mucosal inflammation)
- Redness, swelling, or pain in the mouth (stomatitis)
- Irregular heartbeat, shortness of breath, swelling in the legs, and/or tiredness, which may indicate changes in how your heart pumps blood (left ventricular ejection fraction decreased or left ventricular dysfunction).
  - Tell your study doctor if you get any of these symptoms. Your study doctor will run tests to check your heart is working properly before and during treatment. It is also important to tell your study doctor about any pre-existing heart conditions
- Swelling in the arms or legs as a result of fluid build-up (lymphedema)
- Decreased red blood cells (anemia)
- Increased blood level of a protein from muscle (CPK increased)
- Nose bleeding (epistaxis)
- Redness, chapping, or cracking of the skin
- Redness, tenderness and possibly painful hands and feet (hand and foot syndrome)
- Rash with pus-filled lesions
- Weakness
- Inflammation of hair follicles in the skin (folliculitis)
- Infection of the skin (cellulitis)
- Nail bed changes, nail pain, infection, and swelling of the cuticles (nail disorders, paronychia)
- Shortness of breath or changes in chest CT scan, which may indicate inflammation of the lung (pneumonitis)
  - Tell your study doctor about any pre-existing lung problems that you have
  - If you have signs or symptoms of impaired lung function, your study doctor may order more test(s) to further evaluate your lung function.
- Elevated liver enzymes which may suggest damage to the liver
  - Your study doctor will check liver enzymes regularly while you receive study treatment. Tell your study doctor right away if you experience itching, yellow eyes and/or skin, dark urine, pain, or discomfort in the right upper area of the belly (tummy, stomach).
- Heart rate decreased (bradycardia)

UNCOMMON (RARE) TRAMETINIB SIDE EFFECTS, SOME MAY BE SERIOUS In ***1000*** people receiving trametinib, between 1 and 10 people (0.1 to 1%) may have:
• Symptoms like fever, rash, abnormal liver enzymes and visual changes, which may indicate a hypersensitivity / allergic reaction • Symptoms like shortness of breath, extreme tiredness, and swelling in ankles & legs, which may indicate that your heart is pumping less efficiently (cardiac failure) • Symptoms such as shortness of breath, changes in chest CT scan, which may indicate that inflammation in the lungs (interstitial lung disease) o Tell your study doctor about any pre-existing lung problems that you have o If you have signs or symptoms of impaired lung function, your study doctor may order more test(s) to further evaluate your lung function. • Visual problems (different from above) including: o Retinal detachment o Separation of the light-sensitive membrane in the back of the eye (the retina) from its supporting layers (retinal pigment epithelial detachment, chorioretinopathy) which can result in blurry vision o Symptoms like headache, nausea and vomiting, or vision problems, which may indicate swelling of the optic nerve (papilloedema) o Blockage or bleeding of the vein draining the eye, which in severe cases can lead to vision loss (retinal vein occlusion): o While these types of visual problems often improve, there is a risk that they may not improve. o Detailed eye examination is required at the start of the study. If retinal vein occlusion (see above) is identified, you will not be able to participate in this study.

VERY RARE TRAMETINIB SIDE EFFECTS, MAY BE SERIOUS In ***10000*** people receiving trametinib, between 1 and 10 people (0.1 to 1%) may have::
• Symptoms including muscle pain and kidney damage, which may indicate breakdown of muscle tissue (rhabdomyolysis)

In some cases, side effects can be serious, long-lasting, may never go away, and may lead to death. Cases of sudden death have occurred in patients with advanced cancer.

Certain problems can be dangerous if not treated quickly; call your study doctor right away if you:

- **Feel very tired or faint**
- **Feel pain or sick in your stomach and not want to eat**
- **Bruise easily or develop itching**
- **Have yellow eyes or skin, or dark urine**
- **Become confused**

If you experience certain serious problems (such as an allergic reaction, swelling, difficulty breathing, a bad skin rash, liver or kidney damage, or changes in your heart

beat), you may be asked to return to the clinic for more assessments, which may include more blood tests.

Your study doctor will explain these tests to you if they are needed. You may also need to stop taking the study drug after talking with your study doctor.

You may feel discomfort from some of the procedures during this study.

When you give blood or have a cannula inserted in your arm, you may feel faint, or experience mild pain, bruising, irritation or redness at the site, or blockage of veins. In rare cases, you may get an infection or damage to nerves at the site. A cannula is a small tube that stays in your arm so that you will not need a lot of needle sticks when blood is drawn. Study staff will remove the cannula before you leave the clinic.

When you have your heart monitored, you may have itching or get bruising of the skin where the machine patches are placed.

During some of the tests that may be performed on you (MUGA scans, CT scans, or bone scans), you will be exposed to varying amounts of radiation. Please discuss with your study doctor the amount of radiation for each scan if you have questions. During the CT scans, and MRI, you will get dye that will be injected into one of your veins. There is a risk of allergic reaction to the dye. This reaction may be mild (such as a skin rash or hives) to severe (such as breathing difficulties and shock). There is also a risk that the injection of dyes may cause pain, swelling, bruising, irritation or redness at the site, infection at the site of the needle puncture, or feeling faint. Your study doctor will take steps to prevent this from happening, and may recommend medications that may help with these particular side effects.

Reproductive Risks

For **FEMALE** patients: You should not take part in this study if you are pregnant, as problems with the developing fetus may occur based on studies in animals. Mothers should not breastfeed a baby while on this study and for 4 weeks following the last dose of study drug.

You should not become pregnant while you are in this study because dabrafenib may affect an unborn baby.

If you are a woman who can get pregnant, you will need to have a blood pregnancy test done within 14 days prior to randomization. Women who can get pregnant must agree to use effective contraception for 14 days prior to enrollment, throughout the treatment period and for 6 months after the last dose of study treatment. Check with the study doctor about what kind of birth control methods to use.

Women of childbearing potential should be advised that dabrafenib may decrease the efficacy of hormonal contraceptives and an alternative method of contraception, such as barrier methods, should be used. Check with your study doctor about what kind of birth control methods you should use and how long to use them for.

A double-barrier method includes a condom with spermicide, a diaphragm with spermicide, or a diaphragm and male condom. Another option is to only have intercourse with a partner who has had a vasectomy (surgical sterilization).

If you get pregnant during this study, call the study doctor right away. You will not be able to continue in this study if you become pregnant. You may be asked questions later about the pregnancy and the baby.

For **MALE** patients: Based on studies in animals, dabrafenib may cause damage to the tissue that makes sperm. This may cause sperm to be abnormal in shape and size and could lead to infertility, which may be irreversible.

POTENTIAL BENEFITS

This study offers a possible treatment that might avoid or reduce the extent of eventual surgery.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

Alternatives to taking part in this study include having surgery without receiving dabrafenib or trametinib, taking part in another study or not joining a clinical trial at all. Please speak to your study doctor about these and other alternatives.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

The description of this clinical trial is at NCT02367859.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Depending on your medical needs, photographs of the inside of your eyes (retinas) may be taken, to check for, or help manage the visual side effects of the study drugs. These photographs will not visually identify you, other than in the manner than other medical records and scans identify you. These photographs will only be used for the purposes of this study.

The purpose of this research study is to obtain data or information on the safety and effectiveness of dabrafenib and trametinib; the results will be provided to the sponsor and drug supplier Novartis, Inc; the Food and Drug Administration and other US federal agencies; and governmental agencies in other countries where the study drugs may be considered for approval.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The results from this research study are expected to be presented at scientific or medical meetings or published in scientific journals. If this treatment proves to demonstrate clinical benefit, physicians may adopt dabrafenib in the future as part of the standard treatment for ameloblastoma. You will not be personally identified in the publications, although representatives of the sponsor and FDA and other international regulatory agencies may need to know who you are.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (eg, necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to:

[redacted]
875 Blake Wilbur Drive, 2328
Stanford, California 94305

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to: your name and initials; address; phone number(s); date of birth; age; sex; race; ethnicity; Social Security Number; Medicare ID number; and medical record number (MRN). During the study, researchers will also obtain information about your medical history and medical diagnoses, including family medical history, current and past medications or therapies, physical examination results, laboratory test results (including blood, urine and pregnancy tests), results of procedures (such as CT or MRI scans) and medical reports (such as pathology reports). The researchers will also get information from your medical records.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr A Dimitrios Colevas
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the US Department of Health and Human Services (HHS)
- The Food and Drug Administration
- The National Institutes of Health (NIH)
- The US Centers for Medicare & Medicaid Services (CMS), the agency responsible for administration of the Medicare program
- Novartis and it's authorized agents

- Governmental agencies in other countries where the study drugs may be considered for approval

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on January 1, 2064, or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (eg, if included in your official medical record).

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
If needed: Printed Name of LAR

_____ _____
Signature of LAR Date

_____
LAR's Authority to Act for Participant
(eg, parent, guardian, or conservator)

NOTE: *If using the Short Form Consent process for informed consent in another language pursuant to an "Alteration of HIPAA Authorization," neither the participant nor their LAR should sign the HIPAA "Authorization To Use Your Health Information For Research Purposes" above.*

FINANCIAL CONSIDERATIONS

Payment

You may be provided with reimbursement for your travel expenses for study-required visits (eg, actual costs for lodging and transportation in excess of 50 miles). If you do not complete the study, you will receive reimbursement only for the visits you have completed. Reimbursement will be paid periodically. If you have any questions regarding your reimbursement for participation, please contact the Study Doctor or the study team.

Payments or reimbursement may only be made to US citizens, legal resident aliens, and those who have a work-eligible visa. You may need to provide your Social Security Number (SSN) or equivalent (ie, federal Taxpayer Identification Number, TIN) to receive payment. If your SSN/ TIN is required to receive payment, and you do not wish to provide your SSN/ TIN, you have the option of declining the payment.

Costs

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Support

Novartis Pharmaceuticals is providing study medication (ie, dabrafenib and trametinib) for this study.

COMPENSATION FOR RESEARCH-RELATED INJURY

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for

supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, [redacted] You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact

If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at ([redacted] or toll free at [redacted]. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____
Printed Name of Participant

_____ _____
Signature of Adult Participant Date
If needed:

_____
Printed Name of Legally Authorized Representative (LAR)

_____ _____
Signature of LAR Date

_____
LAR's Authority to Act for Participant
(eg, parent, guardian, or conservator)

Printed Name of Person Obtaining Consent (POC)

_____ _____
Signature of Person Obtaining Consent Date

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short-form foreign language informed consent document.

_____ _____

Signature of witness Date

(eg, staff, translator/interpreter, family member, or other person who speaks both English and the participant's language)
The translated short form must be signed and dated by **BOTH** the participant (or their LAR) **AND** the witness.
The English consent form ("referred to as the "Summary Form" in the regulations"):

- Must be signed by **BOTH** the witness **AND** the Person Obtaining Consent (POC).
- The non-English speaking participant / LAR does **NOT** sign the English consent.
- The non-English speaking participant / LAR should **NOT** sign the HIPAA participant line.
- If the participant / LAR is non-English speaking, the POC must ensure that:
  1) The LAR's Description of Authority is completed, and
  2) Any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.